Prevalence of Spina Bifida and Anencephaly During the Transition to Mandatory Folic Acid Fortification in the United States

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ABSTRACT

Background: In 1992, the United States Public Health Service recommended that all women of childbearing age consume 400 μg of folic acid daily. The Food and Drug Administration authorized the addition of synthetic folic acid to grain products in March 1996 with mandatory compliance by January 1998. The impact of these public health policies on the prevalence of neural tube defects needs to be evaluated. We sought to determine the prevalences of spina bifida and anencephaly during the transition to mandatory folic acid fortification.

Methods: Twenty-four population-based surveillance systems were used to identify 5,630 cases of spina bifida and anencephaly from 1995–99. Cases were divided into three temporal categories depending on whether neural tube development occurred before folic acid fortification (January 1995 to December 1996), during optional fortification (January 1997 to September 1998), or during mandatory fortification (October 1998 to December 1999). Prevalences for each defect were calculated for each time period. Data were also stratified by programs that did and did not ascertain prenatally diagnosed cases.

Results: The prevalence of spina bifida decreased 31% (prevalence ratio [PR] = 0.69, 95% confidence interval [CI] = 0.63–0.74) from the pre- to the mandatory fortification period and the prevalence of anencephaly decreased 16% (PR = 0.84, 95% CI = 0.75–0.95). Stratification by prenatal ascertainment did not alter results for spina bifida but did impact anencephaly trends.

Conclusions: The decline in the prevalence of spina bifida was temporally associated with folic acid fortification of US grain supplies. The temporal association between fortification and the prevalence of anencephaly is unclear.

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INTRODUCTION

Neural tube defects (NTDs) result from the defective closure of the neural tube during early embryogenesis. Spina bifida and anencephaly are the two most common types of NTDs, affecting an estimated 4,000 pregnancies, including 2,500 live births, in the United States (US) each year (Mulinare and Erickson, '97).

Folic acid, a B vitamin, has been shown to reduce the prevalence of NTDs by 50%-70% if taken during the periconceptional period (1–3 months before pregnancy through 12 weeks gestation) (MRC, '91; Czeizel and Dudas, '92). The US Public Health Service and the Food and Nutrition Board of the Institute of Medicine, National Research Council, have recommended that all women of childbearing age who are capable of becoming pregnant consume 400 μg of folic acid daily to reduce their risk of having a baby with an NTD (Centers for Disease Control and Prevention, '92; Institute of Medicine, '98). The US Food and Drug Administration (FDA) established regulations requiring fortifica-

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tion of flour and other enriched grain products with 140 μg of folic acid per 100 g of grain by January 1, 1998 (Food and Drug Administration, '96).

Monitoring temporal trends in the prevalence of NTDs is one method of evaluating the effectiveness of folic acid fortification. Birth certificates are the only data source available at the national level to monitor trends in birth defect prevalences. The use of birth certificates, however, introduces limitations including poor sensitivity for detecting birth defects at birth and no information about birth defects that are prenatally diagnosed and electively terminated (Watkins et al., '96). Case ascertainment methodologies used by population-based surveillance systems can address some of these limitations. Thus, an NTD ascertainment project, using 24 population-based birth defects surveillance programs, was established to determine if prevalences of spina bifida and anencephaly declined during the transition to mandatory fortification of US enriched grain products with folic acid.

METHODS

The Neural Tube Defect Surveillance/Folic Acid Education Committee of the National Birth Defects Prevention Network (NBDPN), with assistance from the Centers for Disease Control and Prevention (CDC), designed an NTD reporting system based on data collected from population-based birth defects surveillance programs. Programs were eligible to participate if they could:

1. Ascertain cases from sources other than birth certificates.
2. Submit data from January 1995 through December 1999 for counts of pregnancies affected by spina bifida without anencephaly (International Classification of Diseases-9- Clinical Modifications [ICD-9-CM] 741.0, 741.9 w/o 740.0-740.1; CDC/BPA 741.00–741.99 w/o 740.0-740.10).
3. Provide annual prevalences of spina bifida and anencephaly in 1995 and 1996.
4. Report data from 1997–99 by quarter of birth: 1st quarter: January–March; 2nd quarter: April–June; 3rd quarter: July–September; and 4th quarter: October–December. Programs were asked to adjust for expected date of delivery for pregnancy terminations and fetal deaths.

Twenty-four states participated in this project (Arkansas, California, Colorado, Delaware, Florida, Georgia, Hawaii, Iowa, Illinois, Kentucky, Maryland, Michigan, Missouri, North Carolina, New Jersey, New York, Oklahoma, Puerto Rico, South Carolina, Texas, Utah, Washington, West Virginia, and Wisconsin). These programs varied in the methods used to identify NTD cases. Many used intensive ascertainment where staff directly abstracted records from various data sources, including hospitals, laboratories, and clinics. Others relied on reports from hospitals, other health care facilities, and private physicians, to obtain case information. Nine of the 24 participating programs ascertained prenatally diagnosed NTD cases as part of their surveillance system (Arkansas, Georgia, Hawaii, Iowa, New York, Oklahoma, Puerto Rico, South Carolina, and Utah). Additional data sources for these programs included prenatal care centers, maternal serum alpha feto-protein diagnostic laboratories, pregnancy termination centers, and specialty clinics. Two programs included prenatal ascertainment for only part of the study period and thus, were excluded from these analyses, leaving 13 programs that did not ascertain prenatally diagnosed and electively terminated cases.

Data reported in this study were counts of spina bifida and anencephaly ascertained by participating programs as of September 2001. Programs were asked to provide the number of cases, including live births, fetal deaths, and elective pregnancy terminations, ascertained by their surveillance system. In addition, programs were asked to provide the total number of births in the population covered by the surveillance system; approximately half of participating programs included fetal deaths or elective pregnancy terminations in addition to live births in the denominator. In this study, prevalence was calculated as the number of spina bifida or anencephaly cases per 10,000 births using the aforementioned definition of cases and births.

Folic acid fortification was authorized by the FDA in March 1996; compliance with fortification mandates was required by January 1998. Thus, data were divided into three temporally defined groups depending on when neural tube development occurred during the transition to mandatory fortification. In this study, data from 1995–96 were referred to as the "pre-fortification" period, data from the first quarter of 1997 through the third quarter of 1998 were referred to as the "optional fortification" period, and data from the fourth quarter of 1998 through the fourth quarter of 1999 were referred to as the "mandatory fortification" period. Prevalences of spina bifida and anencephaly were calculated for these three periods for all 24 participating programs and were calculated separately for the nine programs with and the 13 programs without prenatal ascertainment. The percentage of US births covered was calculated based on the number of live births per month reported by the CDC's National Center for Health Statistics (Curtin and Martin, '00; Ventura et al., '00).

Prevalence ratios (PRs) were calculated by dividing the prevalence from the mandatory fortification period by the prevalence from the pre-fortification period. The Taylor Series method was used to calculate 95% CI for the PRs. Data were analyzed using the Statistical Analysis Battery for Epidemiological Research (SABER) (James, '96).

RESULTS

The prevalences of spina bifida and anencephaly during the pre-, optional, and mandatory fortification periods for all 24 participating programs are shown in Table 1. A 31% decline (PR = 0.69, 95% CI = 0.63–0.74) was observed for spina bifida from the pre- to the mandatory fortification period. The prevalence of anencephaly decreased 16% (PR = 0.84, 95% CI = 0.75–0.95) from the pre- to the mandatory fortification period, however, no decline was observed from the optional to the mandatory fortification period. The prevalences of spina bifida and anencephaly from 1995–99 for all participating programs are presented in Figure 1.

The prevalence of spina bifida decreased 40% (PR = 0.60, 95% CI = 0.51–0.71) among the nine programs with prenatal ascertainment and 28% (PR = 0.72, 95% CI = 0.65–0.80) among the 13 programs without prenatal ascertainment from the pre- to the mandatory fortification period (Table 2). The decline in the prevalence of anencephaly remained significant among programs with prenatal ascertainment (PR = 0.80, 95% CI = 0.66–0.97), however, programs without prenatal ascertainment showed no significant decline (PR = 0.87, 95% CI = 0.75–1.02). Prevalences of spina bifida for programs with and without prenatal ascertainment are shown in Figure 2; data for anencephaly are shown in Figure 3.

DISCUSSION

Data from 24 population-based surveillance programs suggested that the prevalence of spina bifida decreased 31% from the pre- to the mandatory fortification period and that the decline was temporally associated with folic acid fortification. The prevalence of anencephaly declined 16% among all 24 participating programs. No decline, however, was observed between the optional and mandatory fortification periods. When data were stratified by prenatal ascertainment, the trend associated with anencephaly was not observed among programs that did not ascertain prenatally diagnosed cases. It is not clear whether the decline observed among all 24 programs for anencephaly was temporally associated with folic acid fortification.

The decline in the prevalence of spina bifida was significantly different than the decline observed for anencephaly among all 24 participating programs (Breslow-Day test, $P < 0.01$). The difference in the declines remained significant among programs with ($P = 0.02$) and without prenatal ascertainment ($P = 0.04$); no significant trend was observed for anencephaly in the later group. This finding was mirrored in a recent study by Honein et al. ('01) that compared birth prevalences for spina bifida and anencephaly from the mandatory fortification period (October 1998 through December 1999) to the pre-fortification period (October 1995 through December 1996) using data derived from birth certificates. They found that the prevalence of spina bifida decreased 23% (PR = 0.77, 95% CI = 0.70–0.84) whereas anencephaly showed no significant decline (PR = 0.89, 95% CI = 0.78–1.01). The randomized control trials conducted by Czeizel and Dudas

TABLE 1. Prevalences of spina bifida and anencephaly for all 24 participating programs

	Pre-fortification (January 1995–December 1996)			Optional fortification (January 1997–September 1998)			Mandatory fortification (October 1998–December 1999)				
	Total births	% US births	Prevalence (per 10,000)	Total births	% US births	Prevalence (per 10,000)	Total births	% US births	Prevalence (per 10,000)	PR (pre-vs. mandatory)	95% CI
Spina bifida	3,127,161	40.14	5.15	3,063,265	44.77	4.22	2,406,427	48.74	3.54	0.69	0.63–0.74
Anencephaly	3,127,161	40.14	2.43	3,063,265	44.77	2.04	2,406,427	48.74	2.05	0.84	0.75–0.95

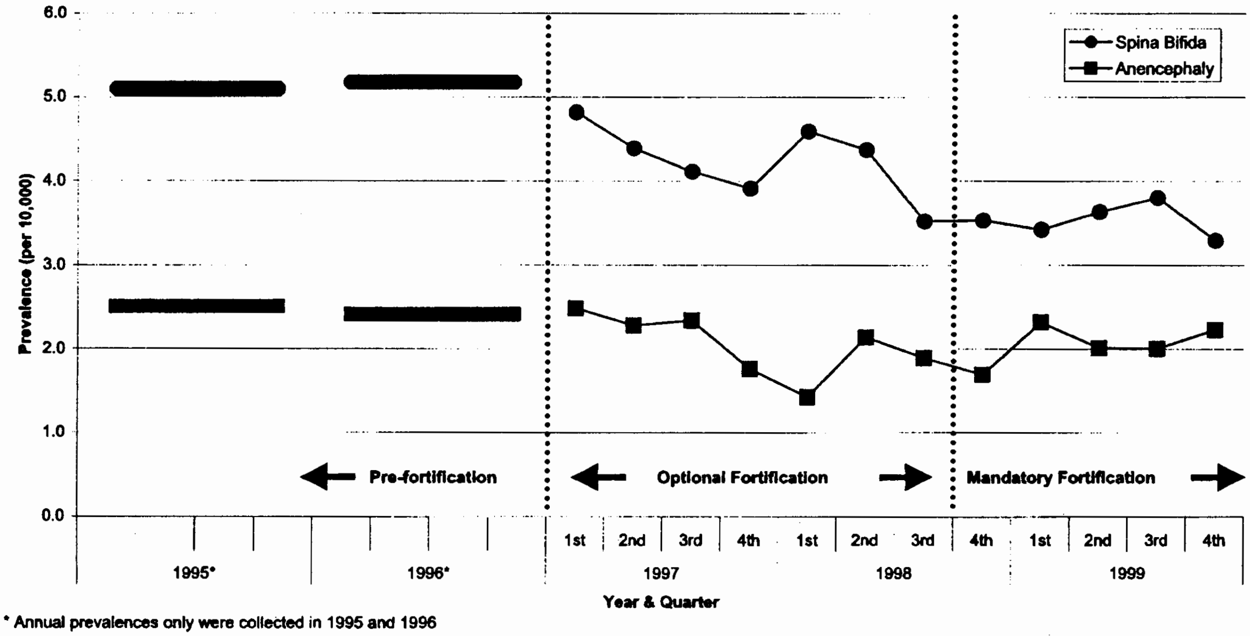

Fig. 1. Prevalences of spina bifida and anencephaly by year and quarter of birth for 24 surveillance programs (1995–99).

('92), and the Medical Research Counsel (MRC) (Medical Research Counsel (MRC) '91) did not indicate that the effect of folic acid differed between anencephaly and spina bifida. These studies were based on approximately 4,500 and 1,200 women, respectively, and thus may have had limited power to detect a difference in the effect of folic acid on these two defects.

The reasons for the divergence between spina bifida and anencephaly results in our study are unclear. The lack of prenatal ascertainment in 13 of the participating programs in our study may have masked a true decline in the prevalence of anencephaly. The trends observed for anencephaly in Figure 3, however, provided some evidence that the decline observed among programs with prenatal ascertainment may have been an artifact. The large drop in the prevalence in anencephaly in 1997 and the subsequent rise in the prevalence in 1998 and 1999 may have been normal fluctuations that resulted in a decline not associated with folic acid fortification. The trend associated with spina bifida remained consistent between programs with and without prenatal ascertainment. Stratification may not have impacted the trend in spina bifida to the extent observed for anencephaly because prenatal diagnosis and subsequent elective termination occurs less frequently for spina bifida cases (Cragan et al., '95). In our study, the prevalence of spina bifida was 38% higher (PR = 1.38, 95% CI = 1.28–1.48) among programs with prenatal ascertainment and the prevalence of anencephaly was two-fold higher (PR = 2.14, 95% CI = 1.95–2.36).

It is also possible that because these defects have multiple etiologies, and thus, may follow the multifactorial/threshold model (Fraser, '98), the combination of factors that results in the development of spina bifida may differ from that for anencephaly. Given differing etiologies, two possible conclusions could be drawn about the relationship between folic acid consumption and these defects. First, the amount of folic acid needed to prevent anencephaly may be higher than the amount needed to prevent spina bifida. The MRC ('91) and Czeizel and Dudas studies ('92) administered 4,000 μg and 800 μg of folic acid to subjects, respectively. The current level of folic acid fortification mandated by the FDA may not be high enough to prevent cases of anencephaly. Second, there may be a smaller percentage of folic acid-preventable anencephaly cases compared to spina bifida and additional fortification would not contribute to the further prevention of this birth defect.

Fortification mandates required the addition of 140 μg of folic acid per 100 g of grain product, which was estimated to increase the median daily consumption of folic acid by 100 μg (Oakley, '98). Recent studies have estimated that the actual amount of folic acid added to enriched grain products exceeds this mandate by approximately 150%. Additionally, it has been estimated that the average amount of cereal actually consumed in a serving is approximately twice the labeled serving size (Whittaker et al., 2001). Daly et al. ('97) found that consumption of 100 μg folic acid daily was associated with a 22% decline in the risk of NTDs, consumption of 200 μg was associated with a 41% decline, and consumption of 400 μg was associated with a 47% decline. These estimates were modified by Wald et al. ('98) who concluded that the consumption of 100, 200, and 400 μg folic acid daily was associated with an 18%, 35%, and

TABLE 2. Prevalences of spina bifida and anencephaly for programs with and without prenatal ascertainment

	Pre-fortification (January 1995–December 1996)			Optional fortification (January 1997–September 1998)			Mandatory fortification (October 1998–December 1999)				
	Total births	% US births	Prevalence (per 10,000)	Total births	% US births	Prevalence (per 10,000)	Total births	% US births	Prevalence (per 10,000)	PR (pre- vs. mandatory)	95% CI
Spina bifida											
Programs with prenatal ascertainment	735,156	9.44	6.68	651,146	9.52	5.41	473,348	9.59	4.04	0.60	0.51–0.71
Programs without prenatal ascertainment	2,173,379	27.90	4.70	2,267,745	33.14	3.90	1,785,684	36.16	3.40	0.72	0.65–0.80
Anencephaly											
Programs with prenatal ascertainment	735,156	9.44	4.18	651,146	9.52	3.44	473,348	9.59	3.36	0.80	0.66–0.97
Programs without prenatal ascertainment	2,173,379	27.90	1.86	2,267,745	33.14	1.69	1,785,684	36.16	1.63	0.87	0.75–1.02

53% decline, respectively, in the prevalence of NTDs. The decline in the prevalence of spina bifida was consistent with the projected consumption of 100–200 μg folic acid daily, however, the decline observed for anencephaly was not consistent with this level of folic acid consumption.

Because the design of this study was ecologic, we could not determine whether individuals with higher intakes of food fortified with folic acid were the underlying reason for the declines observed in our study. Indirect evidence of increased folic acid consumption though fortification can be gleaned from the National Health and Nutrition Examination Survey (NHANES), which indicated that serum folate levels among US women of childbearing age have increased over 200% among non-supplement users from the pre-fortification period (NHANES III, 1988–94) to the mandatory fortification period (NHANES 1999) (Centers for Disease Control and Prevention, '00). Little evidence is available to discern when manufacturers began fortifying products with folic acid. A study of Kaiser Permanente members found that serum folate concentrations changed little from 1994–96, however, and began to increase steadily in 1997, suggesting that women may have been exposed to folic acid fortification during the optional fortification period (Lawrence et al., '99). Assuming that the women included in our analysis also would have experienced increased serum folates during folic acid fortification is not unreasonable.

Although our data were divided into three time periods based on the timing of folic acid fortification, other reasons may contribute to the trends observed in our study. National and state organizations have implemented educational/media campaigns to promote the consumption of folic acid through supplementation. According to a national survey conducted by the Gallup Organization, the percentage of women who consumed supplements containing folic acid daily increased from 28% in 1995 to 32% in 1997 and 1998 (SD ±2) (Centers for Disease Control and Prevention, '95,97,'99). Because of the small change in the percentage of women consuming folic acid-containing supplements from 1995–97 and the lack of change from 1997–98, we speculate that supplement use did not account for the magnitude of the NTD prevalence decline in the observation period.

Under-ascertainment of cases, specifically in the mandatory fortification period could contribute to the observed declines observed in our study. Given that participating programs had approximately 2 years after delivery to ascertain NTD cases, however, the likelihood of the lowered prevalence in the mandatory period being an artifact of under ascertainment seems unlikely. Additionally, three-quarters of the participating programs received funding during the study period to improve their surveillance methods, including ascertainment of NTD cases. Thus, it is possible that these improved methods may diminish the true declines in NTD prevalences during this time period.

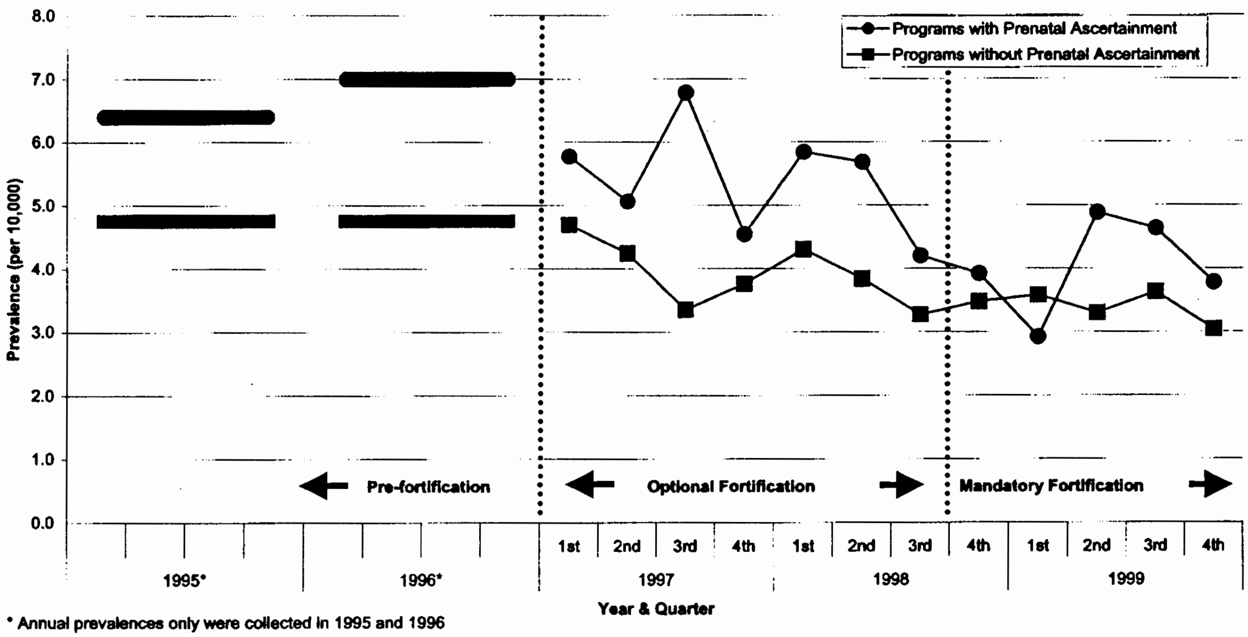

Fig. 2. Prevalences of spina bifida for programs with prenatal ascertainment (9) and programs without prenatal ascertainment (13).

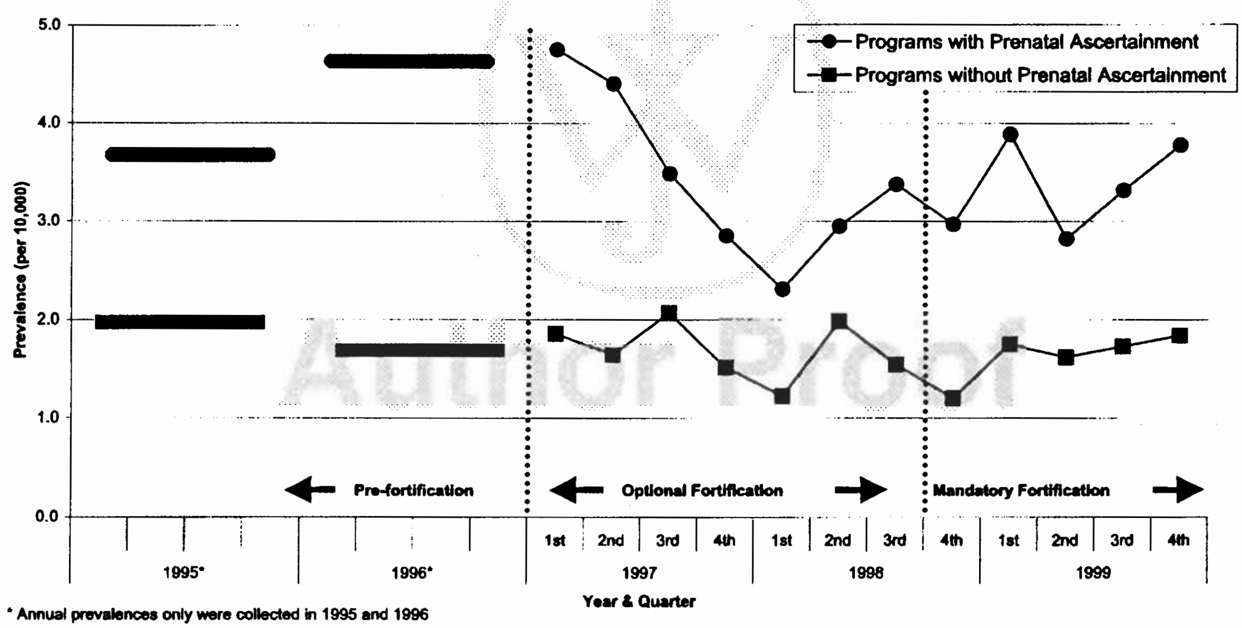

Fig. 3. Prevalence of anencephaly for programs with prenatal ascertainment (9) and programs without prenatal ascertainment (13).

Before fortification of US food supplies, the prevalences of both anencephaly and spina bifida gradually declined in some areas of the US (Yen, '92). These historical declines may affect the results observed in our study, resulting in a coincidental association with the timing of fortification of US food supplies.

These NTD prevalence data, which cover approximately half of the annual US births and include prenatally diagnosed and electively terminated cases, provided a unique assessment of the impact of folic acid fortification on spina bifida and anencephaly prevalences. The transition from pre- to mandatory fortification of the US food supply with folic acid was temporally associated with a decline in the prevalence of spina bifida, though the association was unclear for anencephaly. Further studies that measure women's folic acid intake are needed to confirm the downward trends observed in our study and to assess the causes of these trends.

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